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Dated 7 April 2003

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Patents Form 1/77

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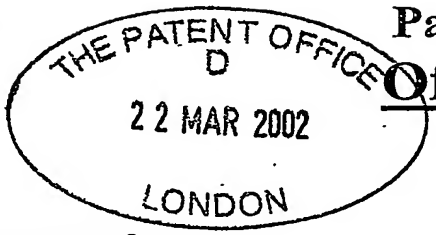

The Patent Office

1/77

25MAR02 E705978-1 C69803
P01/7700 0.00-0206860.9

Request for grant of a patent

(See the notes on the back of this form. You can also get an explanatory leaflet from the Patent Office to help you fill in this form)

The Patent Office
Cardiff Road
Newport
Gwent NP9 1RH

1. Your reference — MA/HG/P33019

2. Patent application number
(The Patent Office will fill in his part) — 22 MAR 2002 — 0206860.9

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

Patents ADP number *(if you know it)* 00473587003

Glaxo Group Limited
Glaxo Wellcome House, Berkeley Avenue,
Greenford, Middlesex UB6 0NN, Great Britain

If the applicant is a corporate body, give the country/state of its incorporation

United Kingdom

4. Title of the invention

5. Name of your agent *(if you have one)*

...tellectual Property

"Address for service" in the United Kingdom to which all correspondence should be sent
(including the postcode)

Patents ADP number *(if you know it)* 07960982003

GlaxoSmithKline
Corporate Intellectual Property CN925.1
980 Great West Road
BRENTFORD
Middlesex TW8 9GS

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or each of these earlier applications and *(if you know it)* the or each application number

Country	Priority application number *(if you know it)*	Date of filing *(day / month / year)*

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application	Date of filing *(day / month / year)*

8. Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer yes if:*

a) any applicant named in part 3 is not an inventor, or
b) there is an inventor who is named as an applicant, or
c) any named applicant is a corporate body
See note (d)

Patents Form 1/77

5 Enter the number of sheets for any of the following items you are filing with this form. Do not count copies of the same document

Continuation sheets of this form	
Description	51
Claim(s)	7
Abstract	1
Drawings	

10. If you are also filing any of the following, state how many against each item.

Priority Documents	
Translations of priority documents	
Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	
Request for preliminary examination and search *(Patents Form 9/77)*	
Request for substantive examination *(Patents Form 10/77)*	
Any other documents *(please specify)*	

11. We request the grant of a patent on the basis of this application

Signature _____ Date 22-Mar-02

M Atkinson

12. Name and daytime telephone number of person to contact in the United Kingdom: M Atkinson 01279 631323

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Compounds

The present invention relates to novel imidazole derivatives, to processes for their preparation, to pharmaceutical compositions containing them and to their use in medicine. More particularly the present invention relates to novel imidazole derivatives which are inhibitors of mitogen and stress activated protein kinase-1 (herein after referred to as Msk-1)

An important mechanism by which cells sense and respond to extracellular stimuli is the activation and modulation of intracellular signal transduction pathways. One of the major signal transduction systems utilized by cells is the MAP kinase signalling pathways. These pathways share a common architecture, consisting of a cascade of protein kinases that are sequentially phosphorylated and activated, resulting in the activation of a MAP kinase (MAPK). Three MAP kinase pathways have been widely characterised: the Erk pathway, which responds to mitogenic stimuli and results in activation of Erk, and the JNK and p38 pathways, which are commonly associated with transducing cellular stress signals and result in activation of JNK and p38 MAPK.

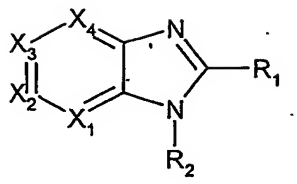
Mitogen and stress-activated protein kinases 1 (Msk1) and 2 (Msk2, also named RSKB or RLPK) constitute a family of kinases that can be phosphorylated and activated by either p38 or Erk. Msks are reported to be localized exclusively to the nucleus, and as such are responsible for the phosphorylation and activation of the transcription factor CREB in response to certain stress stimuli. In macrophage and monocyte cells, Msk1 is involved in CREB-mediated transcriptional regulation of IL-1β and Cox2 in response to bacterial

lipopolysaccharide. In addition, Msk1 can also phosphorylate the nucleosomal proteins histone H3 and HMG14, and thus may have a critical role in linking cellular signalling pathways to chromatin modification and modulation of transcriptional factor complexes. Inhibitors of kinases in the Erk MAP kinase cascade have been suggested for use in the treatment and/or prophylaxis of disorders associated with neuronal degeneration resulting from ischemic events, including cerebral ischemia after cardiac arrest, stroke and multi-infarct dementia and also after cerebral ischemic events such as those resulting from head injury, surgery and/or during childbirth. Since Msks are activated by Erk MAPK, Msk inhibitors could serve a similar use. Although Msks are only one of a number of Erk substrates, CREB is involved in many different transcriptional activities, and Msk-mediated CREB phosphorylation could play a role in some cancers. In addition, through modulation of production of pro-inflammatory cytokines such as IL-1β and prostaglandins, inhibitors of Msks could be of use in treatments for neuroinflam... diseases such as stroke, multiple sclerosis, Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis and inflammatory pain, as well as other inflammatory diseases such as rheumatoid arthritis, irritable bowel syndrome, inflammatory bowel disease and asthma.

WO 97/12615 teaches novel 2-heteroaryl benzimidazole derivatives, which are inhibitors of the specific lipoxygenase enzyme 15-LO.

We have now identified a group of novel imidazole derivatives which are potent inhibitors of the protein kinase Msk-1.

The present invention thus provides compounds of the general formula (I)



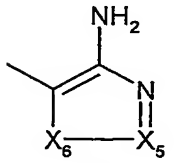
(I)

and physiologically acceptable salts and or N-oxides thereof wherein,

X_1 is N or CR_3; X_2 is N or CR_4; X_3 is N or CR_5; X_4 is N or CR_6.

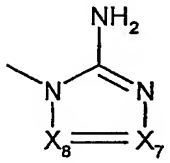
with the proviso that at least one but not more than two of X_1, X_2, X_3 and X_4 represents N.

R_1 is a 5-, or 6- membered heterocyclic group selected from group a, b, c or d



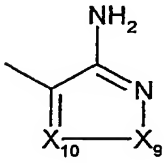
(a)

wherein X_5 is a group selected from N or CR_7 and X_6 is a group selected from O, S or NR_8;



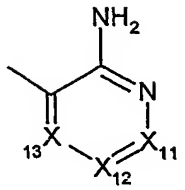
(b)

wherein X_7 and X_8 which may be the same or different is a group selected from N or CR_9;



(c)

wherein X_9 is a group selected from O, S or NR_8 and X_9 is N or CR_{10};



(d)

wherein X_{11}, X_{12} and X_{13} may be the same or different and selected from a group N or CR_{11};

R_2 and R_8 independently represents hydrogen, hydroxy, aryl, heteroaryl, C_{3-7}cycloalkyl, heterocyclyl,a group YR_{12}, $N=R_{13}$, $CONR_{14}R_{15}$, $NHCOR_{16}$, $SO_2NR_{14}R_{15}$ or C_{1-6}alkyl [optionally substituted by a group selected from optionally substituted phenyl, C_{3-7}cycloalkyl, heteroaryl, heterocyclyl, acylamino, NH_2, $R_{19}NH$, $R_{19}R_{20}N$, $SO_2NR_{14}R_{15}$, $CONR_{14}R_{15}$, $NHCOR_{16}$ or $NR_{17}SO_2R_{18}$ group];

R_3, R_4, R_5,R_6,R_7,R_9,R_{10} and R_{11} independently represent a group selected from hydrogen, halogen, hydroxy, $R_{19}O$, $R_{19}S(O)_n$, NH_2, $R_{19}NH$, $R_{19}R_{20}N$, nitro, formyl, C_{1-4}alkanoyl, optionally substituted phenyl, heteroaryl, cycloalkyl, cycloalkylalkyl, aryloxy, heteroaryloxy, heterocyclyl, $CONR_{15}R_{13}$, $NHCOR_{16}$, $SO_2NR_{14}R_{15}$, $NR_{17}SO_2R_{18}$ or C_{1-6}alkyl [optionally substituted by a group selected from optionally substituted phenyl, C_{3-7}cycloalkyl, heteroaryl, heterocyclyl, NH_2, $R_{19}NH$, $R_{19}R_{20}N$, acylamino, hydroxy, $CONR_{14}R_{15}$, $NHCOR_{16}$, $SO_2NR_{14}R_{15}$ or $NR_{17}SO_2R_{20}$ group];

Y represents O, NH or $S(O)_n$;

R_{12} represents aryl, heteroaryl, cycloalkyl, heterocyclyl or C_{1-6}alkyl [optionally substituted by a group selected from optionally substituted phenyl, C_{3-7}cycloalkyl, heteroaryl, heterocyclyl, NH_2, $R_{19}NH$, $R_{19}R_{20}N$, acylamino, hydroxy, $CONR_{14}R_{15}$, $NHCOR_{16}$, $SO_2NR_{14}R_{15}$ or $NR_{17}SO_2R_{18}$ group];

R_{13} represents an alkylidene group which may be substituted by an aryl, heteroaryl, heterocyclyl or cycloalkyl group or R_{13} represents a cycloalkylidene or heterocycloalkylidene group.

R_{14} and R_{15} independently represent hydrogen, aryl, heteroaryl, cycloalkyl or C_{1-6}alkyl [optionally substituted by a group selected from optionally substituted phenyl, C_{3-7}cycloalkyl, heteroaryl, heterocyclyl, NH_2, $R_{19}NH$, $R_{19}R_{20}N$, or acylamino group] or R_{14} and R_{15} together with the nitrogen atom to which they are attached form a 4-7 heterocyclic ring which may be saturated or unsaturated and optionally contains another heteroatom selected from O,N or $S(O)_n$;

R_{16} and R_{18} independently represent ,aryl, heteroaryl, heterocyclyl,cycloalkyl or C_{1-6}alkyl [optionally substituted by a group selected from optionally substituted phenyl, C_{3-7}cycloalkyl, heteroaryl, heterocyclyl, NH_2, $R_{19}NH$, $R_{19}R_{20}N$, or acylamino group] or the [illegible] wherein R_{14} and R_{15} have the meanings defined above;

R_{17} represents hydrogen, aryl, heteroaryl, cycloalkyl or C_{1-6}alkyl [optionally substituted by a group selected from optionally substituted phenyl, C_{3-7}cycloalkyl, heteroaryl, heterocyclyl, NH_2, $R_{19}NH$ $R_{19}R_{20}N$, or acylamino group];

R_{19} and R_{20} independently represent a group selected from C_{1-6} alkyl, C_{3-7}cycloalkyl, C_{3-7}cycloalkylalkyl, aryl, aralkyl, heteroaryl, heteroarylalkyl, heterocyclyl or heterocyclylalkyl;

n is zero, 1 or 2.

It will be appreciated that any of the substituents R_1 to R_{20} as defined in formula (1) above may contain at least one asymmetric center and it is to be understood that the invention includes all possible enantiomers arising there from and mixtures thereof including racemates.

The term alkyl as a group or part of a group e.g. alkoxy, alkylthio,alkylamino or dialkylamino refers to a C_{1-6} straight or branched chain alkyl group.

The term halogen includes fluorine, chlorine, bromine or iodine.

The term aryl as a group or part of a group e.g. aryloxy,aralkyl or arylamino refers to an optionally substituted phenyl or fused bicyclic aryl group e.g. naphthyl.

The terms aryl, optionally substituted phenyl, heteroaryl, and 4-7 membered heterocyclyl as a group or part of a group includes such groups which are optionally substituted with 1 to 3 substituents which may be the same or different and selected from halogen, aryl, heteroaryl, heterocyclylalkyl, hydroxy, alkyl, amino, alkylamino , dialkylamino, arylamino, heteroarylamino, heterocyclylamino, acylamino, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, acylaminoalkyl, arylaminoalkyl, heteroarylaminoalkyl,cycloalkylaminoalkyl, carboxy, carboxamido,alkoxycarbonyl, aminoalkoxy, dialkylaminoalkoxy, acylaminoalkoxy ,sulphonamido, aminosulphon cyano, nitro, $R_{21}O$ or $R_{21}S(O)_n$ wherein R_{21} is a group selected from alkyl, aryl, heteroaryl or heterocyclylalkoxy and n is zero, one or two, or each of the said groups form part of a fused bicyclic ring system containing up to 10 ring members and which is at least partially saturated.

The term heteroaryl as a group or part of a group e.g. heteroaryloxy refers to a 5, or 6 membered ring or a fused 6,5 or 6,6 bycyclic ring system.

When heteroaryl represents a 5 membered group it contains a heteroatom selected from O, N or S and may optionally contain a further 1 to 3 nitrogen atoms. Examples of such groups include furanyl, thienyl, isoxazolyl, oxazolyl or imidazolyl.

When heteroaryl represents a 6-membered group it contains from 1 to 3 nitrogen atoms. Examples of such groups include pyridyl, pyrimidinyl, or triazinyl.

The term 5,6 fused bicyclic heteroaryl group refers to a group in which the 5-membered ring contains an oxygen, sulphur or NH group and the 6 membered ring optionally contains from 1 to 3 nitrogen atoms. Examples of such groups include benzofuranyl , benzothienyl or indolyl.

The term 6,6 fused bicyclic heteroaryl group refers to a bicyclic heteroaryl group which contains at least one nitrogen atom in one of the rings and may contain up to 3 nitrogen atoms in each ring. Examples of such groups include quinolinyl, isoquinolinyl or naphthyridinyl.

The term heterocyclyl as a group or part of a group such as heterocyclylalkyl, heterocyclylalkylidene refers to a 4-7 membered heterocyclyl group which is linked to rest of the compound of formula (1) via a carbon or nitrogen atom in that group and which contains one or two hetero atoms selected from N, O or S, and when the heterocyclyl group contains a ring member NH or the heterocyclyl group is subtituted by a primry or secondary amino group then the term also includes N-acyl derivatives thereof.

The term cycloalkyl as a group or part of a group e.g. cycloalkylalkyl or cycloalkylidene refers to a 3-7 membered carbocyclic group.

The term fused bicyclic ring system containing up to 10 ring members and which is at least partially saturated includes carbocyclic and heterocyclic 6,5 and 6,6 bicyclic ring systems. Examples of such 6,5 and 6,6 carbocyclic ring systems include those wherein the bicyclic ring comprises a benzene ring fused to a 5 or 6 membered carbocyclic ring which is at least partially saturated e.g. tetrahydronaphthyl,indanyl or indenyl. Examples of such 6,5, or 6,6 heterocyclic rings include those wherein one ring is benzene which is fused to a 5 or 6 membered ring containing one or two hetero atoms selected from O, S or N e.g. indolinyl, isoindolinyl, dihydrobenzofuranyl, dihydrobenzothienyl, 1,3-

benzodioxolyl, benzopyrrolyl, 1,3-benozodithiolyl, 1,4-benzodioxanyl, chromanyl or chromenyl .

The term acyl as a group or part of the acylamino group referes to an alkanoyl, aroyl, aralkanoyl, alkoxycarbonyl, aryloxycaronyl or aralkoxycarbonyl group.

The compounds of formula (I) form salts with inorganic and organic acids and the invention includes such salts formed with physiologically acceptable inorganic and organic acids.

The compounds of formula (I), form N-oxides. Thus, the compound of formula(I) wherein X_3 is N or X_2 is N forms an N oxide and the invention includes such compounds.

A preferred class of compounds of formula (I) are those wherein only one of X_1, X_2, X_3 or [illegible] Within this class conveniently X_2 or X_3 represent N or more particularly X_3 represents N.

A further preferred class of compounds are those wherein X_1 and X_3 each represents N.

A further preferred class of compounds of formula (I) are those wherein R_1 is a group selected from (c) or (d).

When R_1 is the group (c) this is conveniently a group wherein X_9 is oxygen and X_{10} is nitrogen or X_9 is NR_8 wherein R_8 is hydrogen or methyl and X_9 is CH

When R_1 is the group (d) this is conveniently a group wherein X_{11} and X_{12} each represent CH and X_{13} is the group CH or N.

The group R_1 is preferably a group (c) wherein X_9 is oxygen and X_{10} is nitrogen.

Examples of suitable R_2 groups include hydrogen, C_{1-6}alkyl such as methyl, ethyl, isopropyl, sec butyl and 2-ethylbutyl, C_{3-7} cycloalkyl e.g. cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, C_{3-7}cycloalkylalkyl e.g. C_{3-7} cycloalkylmethyl such as cyclopropylmethyl or cyclohexylmethyl, optionally substituted phenyl such as phenyl or phenyl (substituted by an amino, aminomethyl, diethylaminoethoxy, methoxy or hydroxy group), alkyl (substituted by hydroxy e.g. 2-hydroxy-1-methyl-ethyl), alkyl (substituted by amino, acylamino , $R_{19}NH$ or $R_{19}R_{20}N$ e.g. 4-aminobutyl, 2-dimethylamino-1-methylethyl, 4-diethylamino-1-methyl- butyl or 4-butyloxycarbonylamino-butyl) or a 4-7 membered heterocyclyl group e.g.4-piperidinyl.

When X_2 is CR_4 then the group R_4 is conveniently hydrogen, methyl or alkoxy e.g, methoxy.

When X_3 is CR_5 then R_5 is coveniently hydrogen, alkyl e.g. methyl or alkoxy e.g. methoxy.

Wherein X_4 is CR_6 the group R_6 is conveniently hydrogen, halogen e.g. chlorine , alkyl e.g, methyl,alkoxy e.g.methoxy, optionally substituted phenyl e.g. phenyl or a 4-7 membered heterocyclyl group e.g. 1- pyrrolidinyl.

Wherein X_1 is the group CR_3 then R_3 is conveniently hydrogen, halogen e.g. e.g. bromine,optionally substituted phenyl e.g. phenyl or phenyl (substituted by methoxy, aminomethyl, cyano, formyl, aryloxy e.g. phenoxyor halogen e.g. fluorine), an heteroaryl group (e.g thienyl such as 2-thienyl or 3-thienyl, 2-furanyl, pyridyl such as 3-pyridyl or 4-pyridyl, 3,5-dimethylisoxazol-4-yl , indolyl,or 8-quinolinyl), alkyl e.g. methyl (substituted by the group $R_{19}NH$ e.g. R_{19} is aralkyl such as an optionally substituted benzyl group e.g. 4- bromobenzyl or 3-methoxybenzyl) or alkyl e.g. methyl substituted

by a 4-7 membered heterocyclyl group e.g 1- piperazinylmethyl or a 6,5-fused bicycloheterocyclyl e.g. 5-benzo[1,3]dioxolyl.

Specific preferred compounds according to the invention include:

4-(1-Ethyl-1*H*-imidazo[4,5-*c*]pyridin-2-yl)furazan-3-ylamine;

4-(1-Cyclopropyl-1*H*-imidazo[4,5-*c*]pyridin-2-yl)furazan-3-ylamine ;

4-(1-Methyl-1*H*-imidazo[4,5-*c*]pyridin-2-yl)furazan-3-ylamine;

4-(1-Cyclohexyl-1*H*-imidazo[4,5-*c*]pyridin-2-yl)furazan-3-ylamine;

4-(1-Cyclopropylmethyl-1*H*-imidazo[4,5-*c*]pyridin-2- yl)furazan-3-ylamine;

4-(1-Cyclohexylmethyl-1*H*-imidazo[4,5-*c*]pyridin-2- yl)furazan-3-ylamine;

4-(1-Cyclobutyl-1*H*-imidazo[4,5-*c*]pyridin-2- yl)furazan-3-ylamine;

4-[1-(2-Ethylbutyl)-1*H*-imidazo[4,5-*c*]pyridin-2- yl)furazan-3-ylamine;

4-(-Isopropyl-1*H*-imidazo[4,5-*c*]pyridin-2- yl)furazan-3-ylamine;

4-(1-*sec*-Butyl-1*H*-imidazo[4,5-*c*]pyridin-2- yl)furazan-3-ylamine;

4-(1-Cyclopentyl-1 *H*-imidazo[4,5-c] pyridin-2-yl)-furazan-3-ylamine;

4-(1-Cycloheptyl-1 *H*-imidazo[4,5-c] pyridin-2-yl-furazan-3-ylamine;

4-[1-(2-Dimethylamino-1-methylethyl)-1*H*-imidazo[4,5-*c*]pyridin-2- yl)furazan-3-ylamine;

4-(1-Piperidin-4-yl)-1- *H*-imidazo[4,5-c] pyridin-2-yl-furazan-3-ylamine;

4-[1-(4-Diethylamino-1-methyl-butyl)-1 *H* -imidazo[4,5- *c*]pyridin-2-yl]-furazan-3-ylamine;

{4-[2-(4-Amino-furazan-3-yl)-imidazo[4,5-*c*]pyridin-1-yl]-butyl}-carbamic acid tert-butyl ester;

(+)-4-[1-(2-Dimethylamino-1-methylethyl)-1*H*-imidazo[4,5-*c*]pyridin-2- yl)furazan-3-ylamine;

(-)-4-[1-(2-Dimethylamino-1-methylethyl)-1-*H*-imidazo[4,5-*c*]pyridin-2- yl)furazan-3-ylamine;

4-[1-(4-Methoxy-phenyl)-1*H*-imidazo[4,5-*c*]pyridin-2-yl]-furazan-3-ylamine;

4-(1-Phenyl-1 *H* -imidazo[4,5- *c*]pyridin-2-yl)-furazan-3-ylamine;

4-[1-(4-Amino-phenyl)-1H-imidazo[4,5-*c*]pyridin-2-yl]-furazan-3-ylamine;

4-[2-(4-Amino-furazan-3-yl)-imidazo[4,5-c]pyridin-1-yl]-phenol;

4-{1-[4-(2-Dimethylamino-ethoxy)-phenyl]-1 *H* -imidazo[4,5- *c*]pyridin-2-yl}-furazan-3-ylamine ;

4-[1-(4-Amino-butyl)-1 *H* -imidazo[4,5- *c*]pyridin-2-yl]-furazan-3-ylamine;

4-(7-Bromo-1-ethyl-1*H*-imidazo[4,5-*c*]pyridin-2-yl)furazan-3-ylamine

4-(1-Ethyl-7-phenyl-1*H*-imidazo[4,5-*c*]pyridin-2-yl)furazan-3-ylamine;

4-[1-Ethyl-7-(4-methoxyphenyl)-1*H*-imidazo[4,5-*c*]pyridin-2-yl]furazan-3-ylamine

4-(1-Ethyl-7-thiophen-2-yl-1*H*-imidazo[4,5-*c*]pyridin-2-yl)furazan-3-ylamine;

4-[7-(4-Aminomethylphenyl)-1-ethyl-1*H*-imidazo[4,5-*c*]pyridin-2-yl]furazan-3-ylamine;

4-(1-Ethyl-5-oxy-1*H*-imidazo[4,5-*c*]pyridin-2-yl)furazan-3-ylamine;

4-(4-Chloro-1-ethyl-1*H*-imidazo[4,5-*c*]pyridin-2-yl)furazan-3-ylamine;

4-(1-Ethyl-4-phenyl-1*H*-imidazo[4,5-*c*]pyridin-2-yl)furazan-3-ylamine;

3-(1-Ethyl-1 *H*-imidazo[4,5-*c*]pyridin-2-yl)-pyrazin-2-ylamine;

3-(1-Ethyl-1 *H*-imidazo[4,5-*c*]pyridin-2-yl)-pyridin-2-ylamine;

4-(1-Ethyl-1*H*-imidazo[4,5-*c*]pyridin-2-yl)-1*H*-pyrazol-3-ylamine;

4-(1-Ethyl-1*H*-imidazo[4,5-*c*]pyridin-2-yl)-1-methyl-1*H*-pyrazol-3-ylamine;

[4-(1-Ethyl-1*H*-imidazo[4,5-*c*]pyridin-2-yl)-1-methyl-1*H*-pyrazol-3-yl]-carbamic acid *tert*-butyl ester;

4-(1-Ethyl-1*H*-imidazo[4,5-*c*]pyridin-2-yl)-1-methyl-1*H*-pyrazol-3-ylamine;

4-(1-Ethyl-7-piperazin-1-ylmethyl-1H-imidazo[4,5-c]pyridin-2-yl)-furazan-3-ylamine

1-[2-(4-Amino-furazan-3-yl)-1-ethyl-1*H*-imidazo[4,5-c]pyridin-7-ylmethyl]-piperidin-4-ylamine

[2-(4-Amino-furazan-3-yl)-1-ethyl-1*H*-imidazo[4,5-c]pyridin-7-ylmethyl]-piperidin-4-yl-amine

4-{7-[(4-Bromo-benzylamino)-methyl]-1-ethyl-1*H*-imidazo[4,5-c] pyridin-2-yl}-furazan-3-ylamine

4-{1-Ethyl-7-[(3-methoxy-benzylamino)-methyl]-1*H*-imidazo[4,5-c]pyridin-2-yl}-furazan-3-ylamine

4-(1-Ethyl-4-methyl-1*H*-imidazo[4,5-c]pyridin-2-yl)-furazan-3-ylamine;

4-(1-Ethyl-7-furan-3-yl-1*H*-imidazo[4,5-*c*]pyridin-2-yl)furazan-3-ylamine;

4-(1-Ethyl-7-thiophen-3-yl-1*H*-imidazo[4,5-*c*]pyridin-2-yl)furazan-3-ylamine;

4-[1-Ethyl-7-(3-methoxyphenyl)-1*H*-imidazo[4,5-*c*]pyridin-2-yl]furazan-3-ylamine;

4-[1-Ethyl-7-(1-methyl-1*H*-pyrazol-5-yl)-1*H*-imidazo[4,5-*c*]pyridin-2-yl]furazan-3-ylamine;

4-[1-Ethyl-7-(4-fluorophenyl)-1*H*-imidazo[4,5-*c*]pyridin-2-yl]furazan-3-ylamine;

4-(7-Benzo[1,3]dioxol-5-yl-1-ethyl-1*H*-imidazo[4,5-*c*]pyridin-2-yl)furazan-3-ylamine;

4-[1-(3-Aminopropyl)-1*H*-imidazo[4,5-*c*]pyridin-2-yl]-furazan-3-ylamine;

4-[2-(4-Aminofurazan-3-yl)-1-ethyl-1*H*-imidazol[4,5-*c*]pyridin-7-yl]benzaldehyde;

4-[1-(4-Aminomethylphenyl)-1*H*-imidazo[4,5-*c*]pyridin-2-yl]-furazan-3-ylamine;

4-(1-Ethyl-7-pyridin-4-yl-1*H*-imidazo[4,5-*c*]pyridin-2-yl)furazan-3-ylamine;

4-(1-Ethyl-7-pyridin-3-yl-1*H*-imidazo[4,5-*c*]pyridin-2-yl)furazan-3-ylamine;

4-(1-Ethyl-7-quinolin-8-yl-1*H*-imidazo[4,5-*c*]pyridin-2-yl)furazan-3-ylamine;

4-[7-(3,5-Dimethylisoxazol-4-yl)-1-ethyl-1*H*-imidazo[4,5-*c*]pyridin-2-yl]furazan-3-ylamine;

3-[2-(4-Aminofurazan-3-yl)-1-ethyl-1*H*-imidazol[4,5-*c*]pyridin-7-yl]benzonitrile;

4-[1-(2-Amino-1-methylethyl)-1*H*-imidazo[4,5-*c*]pyridin-2-yl]-furazan-3-ylamine;

4-(1-Cyclopropyl-6-methyl-1*H*-imidazo[4,5-*c*]pyridin-2-yl)furazan-3-ylamine ;

4-[1-(2-Methoxy-phenyl)-1*H*-imidazo[4,5-*c*]pyridin-2-yl]-furazan-3-ylamine;

4-[7-(4-Aminomethylphenyl)-1-cyclopropyl-1*H*-imidazo[4,5-*c*]pyridin-2-yl]furazan-3-ylamine;

4-(9-Cyclopropyl-2-methylsulfanyl-9*H*-purin-8-yl)furazan-3-ylamine;

and physiologically acceptable salts thereof.

The ability of the compounds of formula (I) to antagonise the effect of the kinase Msk-1 may be determined using published procedures such as those described in WO9967283 and WO0127315. Alternatively using the following *in vitro* assay may be used .

Thus the Msk-1 antagonist activity was determined using human recombinant Msk-1 expressed in Sf9 cells (WO9967283). The enzyme underwent prior activation by incubation with MAPK (p42), which was removed prior to storage and subsequent assay. The assay of Msk-1 activity involved incubation with peptide substrate and ATP^{33}, the subsequent incorporation of P^{33} into the peptide was quantified by Scintillation Proximity Assay (SPA - Amersham Pharmacia).

For IC50 determination, test compounds were typically dissolved at 10mM in 100% DMSO, with subsequent serial dilution into 10% DMSO. Compounds were typically assayed over an eleven point dilution range with a concentration in the assay of 10uM to 3nM, in duplicate. IC50 values were calculated by bespoke curve fitting software.

Assays were performed in clear bottomed, white walled, 384 well plates, in a total assay volume of 12.5ul. The assays contained: 2nM activated MSK1; 2uM biotinylated peptide (biotin-GRPRTSSFAEG-OH); 20uM ATP; 25Bq per pmole ATP^{33}; 50mM Hepes; 10mM $MgCl_2$; 0.1mM EDTA; 0.0025% Tween-20; 5mM β-Mercaptoethanol; pH 7.5. The reactions were incubated at 20°C for 60 minutes, then terminated by the addition of 10ul of 200mM EDTA.

Streptavidin PVT SPA beads were added to a concentration of 0.2mg per well. The plates were shaken for 10 minutes before centrifugation at 2500 rpm for 10 minutes. P^{33} incorporation was quantified by scintillation counting in a Wallac Trilux.

The compounds of the invention are therefore useful in the treatm[illegible] of diseases and/or conditions mediated through the kinase Msk-1. Thus [illegible]nds are useful for the treatment or prophylaxis of disorders associated with neuronal degeneration resulting from ischemic events or inflammatory conditions. Examples of such disorders include acute stroke e.g. cerebral stroke, thromboembolic stroke, hemorrhagic stroke and cerebral ischemia, multi infarct dementia , pain, arthritis e.g. rheumatoid arthritis, osteoarthritis, psoriasis, and enteropathic arthritis, multiple sclerosis, Alzheimers disease, Parkinson's disease, amyotrophic lateral sclerosis, spinal cord injury and asthma. The compounds may also be useful for the treatment of irritable bowel syndrome, inflammatory bowel disease and certain cancers.

The invention therefore provides for the use of a compound of formula (I) and/or physiologically acceptable salts thereof for use in therapy and in particular for use as a medicine for inhibiting the effects of the kinase Msk-1.

The invention also provides for the use of a compound of formula (I) and/or a physiologically acceptable derivative or salt thereof for the manufacture of a medicament for inhibiting the effects of the kinase Msk-1.

According to a further aspect, the invention also provides for a method for inhibiting the effects of the kinase Msk-1 in a mammal e.g. a human , comprising administering to a patient in need thereof an effective amount of a compound of formula (I) and/or a physiologically acceptable derivative

It will be appreciated by those skilled in the art that reference herein to treatment extends to prophylaxis as well as the treatment of established diseases or symptoms.

It will further be appreciated that the amount of a compound of the invention required for use in treatment will vary with the nature of the condition being treated, the route of administration and the age and the condition of the patient and will be ultimately at the discretion of the attendant physician. In general however doses employed for adult human treatment will typically be in the range of 5 to 800mg per day, dependent upon the route of administration.

Peferred routes of administration include intravenous injection or orally.

Thus for parenteral administration a daily dose regimen will typically be in the range 0.1 to 80mg/kg of the total body weight, preferably from about 0.2 to 30mg /kg or more preferably 0.5 to 15mg/kg.. For oral administration a daily dose regimen will typically be within the range range 0.1 to 80mg/kg of the total body weight, preferably from about 0.2 to 30mg /kg or more preferably 0.5 to 15mg/kg

The desired dose may conveniently be presented in a single dose or as divided doses administered at appropriate intervals, for example as two, three, four or more sub-doses per day.

While it is possible that, for use in therapy, a compound of the invention may be administered as the raw chemical, it is preferable to present the active ingredient as a pharmaceuti[illegible]

The invention thus further provides a pharmaceutical formulation comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof together with one or more pharmaceutically acceptable carriers thereof and, optionally, other therapeutic and/or prophylactic ingredients. The carrier(s) must be 'acceptable' in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

The compositions of the invention include those in a form especially formulated for oral, buccal, parenteral, inhalation or insufflation, implant or rectal administration.Appropriate dosage forms for adminisration by each of these routes may be prepared by conventional techniques.

Tablets and capsules for oral administration may contain conventional excipients such as binding agents, for example, syrup, acacia, gelatin, sorbitol, tragacanth, mucilage of starch or polyvinylpyrrolidone; fillers, for example, lactose, sugar, microcystalline cellulose, maize-starch, calcium phosphate or sorbitol; lubricants, for example, magnesium stearate, stearic acid, talc, polyethylene glycol or silica; disintegrants, for example, potato starch or sodium starch glycollate, or wetting agents such as sodium lauryl sulphate. The tablets may be coated according to methods well known in the art. Oral liquid preparations may be in the form of, for example, aqueous or oily suspensions, solutions emulsions, syrups or elixirs, or may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, for example, sorbitol syrup, methyl cellulose, glucose/sugar syrup, gelatin, hydroxyethylcellulose, carboxymethyl cellulose, aluminium stearate gel or hydrogenated edible fats; emulsifying agents, for example, lecithin, sorbitan mono-oleate or acacia; non-aqueous vehicles (which may include edible oils), for example, almond oil, fractionated coconut oil, oily esters, propylene glycol or ethyl alcohol; solubilizers such as surfactants for example polysorbates or other agents such as cyclodextrins; and preservatives, for example, methyl or propyl p-hydroxybenzoates or ascorbic acid. The compositions may also be formulated as suppositories, e.g. containing conventional suppository bases such as cocoa butter or other glycerides.

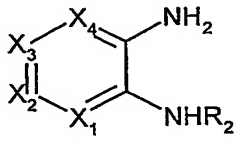
For buccal administration the composition may take the form of tablets or lozenges formulated in conventional manner.

The composition according to the invention may be formulated for parenteral administration by injection or continuous infusion. Formulations for injection may be presented in unit dose form in ampoules, or in multi-dose containers with an added preservative. The compositions may take such forms as suspensions, solutions, or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilising and/or dispersing agents. Alternatively the active ingredient may be in powder form for constitution with a suitable vehicle, e.g. sterile, pyrogen-free water, before use.

Coveniently the compounds of the invention are formulated for intravenous or oral administration.

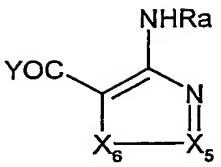
The compositions according to the invention may contain between 0.1-99% [illegible] active ingredient, conveniently from 30-95% for tablets and capsules and 3-[illegible] preparations.

Compounds of formula (I) wherein R_1 is a group (a), (c) and (d) may be prepared by reacting the diamine (II)

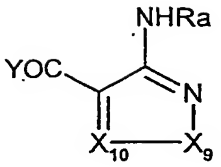


(II)

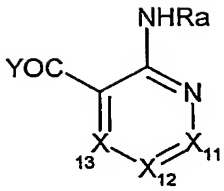
wherein R_2, X_1, X_2, X_3 and X_4 have the meanings defined in (I) with the appropriate compound of formula (III), (IV) or (V)



(III)



(IV)



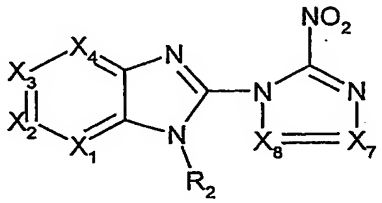
(V)

wherein Y is hydrogen , halogen e.g. Cl, Br or I, hydroxy or C_{1-4}alkoxy, Ra is hydrogen or a nitrogen protecting group such as an alkoxycarbonyl or benzyloxycarbonyl group and each of X_5, X_6, X_9, X_{10}, X_{11}, X_{12} and X_{13} have the meanings as defined in formula (I) or is a group available thereto, followed when required by removal of the nitrogen protecting group Ra using conventional methods.

When Y is a group selected from halogen, alkoxy or hydroxy the reaction is carried out with heating and optionally in the presence of a solvent and/or a dehydrating agent such as polyphosphoric acid.

When Y is hydrogen the reaction is conveni[illegible] carried out in the presence of an oxidant such as sodium bisulphite.

Compounds of formula (I) wherein Y is the group (b) may be prepared by reduction of the corresponding nitro derivative (VI)

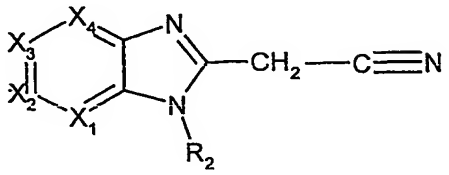


(VI)

wherein R_2, R_3, R_3, X_1, X_2, X_3, X_4, X_7 and X_8 have the meanings defined in formula (I).

The reduction may be effected using conventional procedures for converting a nitro group into an amino group, thus for example the reduction may be effected using hydrogen and a suitable metal catalyst e.g. palladium.

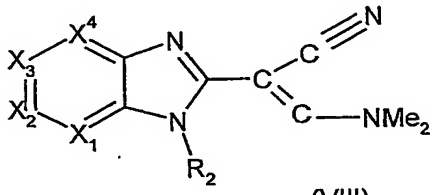
Compounds of formula (I) wherein R_1 is the group (c) and X_9 is oxygen and X_{10} is nitrogen may be prepared by reacting the nitrile (VII)



(VII)

wherein R_2, X_1, X_2, X_3 and X_4 have the meanings defined in formula (I) with hydrochloric acid and sodium nitrite in a solvent such as an alkanol and treatment of the product thus formed with a base e.g. aqueous sodium hydroxide and hydroxylamine and subsequent heating.

Compounds of formula (I) wherein R_1 represent the group (c) wherein X_9 is NH and X_{10} is CH may be prepared by reacting compound (VIII)



(VIII)

wherein R_2, X_1, X_2, X_3 and X_4 have the meanings defined in formula (I) with hydrazine. This reaction is preferably carried out in a solvent e.g. an alkanol such as methanol and with heating.

In another aspect of the invention compounds of formula (I) may be converted into other compounds of formula (I).

Thus N-oxides of compounds of formula (I) may be prepared by treating a compound of formula (I) with a peroxy acid such as hydrogen peroxide in acetic acid.

For example reactions of a compound of formula (I) wherein X_2 or X_3 is N may be converted into the corresponding N-oxide i.e. X_2 or X_3 is N=O by reaction with hydrogen peroxide in acetic acid.

A compound of formula (I) wherein R_3 or R_6 is halogen e.g. chlorine or bromine may be prepared from the of formula (I) wherein X_2 is N=O and X_1 is CH or X_3 is N=O and X_4 is CH by reaction with the appropriate phosphorus oxyhalide e.g. phosphorus oxychloride or oxybromide.

Compounds of formula (I) wherein R_3 or R_6 is an optionally substituted phenyl group may be prepared by treating the corresponding compound wherein R_3 and or R_6 is halogen e.g. chlorine or bromine by reaction with the corresponding optionally substituted phenylboronic acid in the presence of bis(triphenylphosphine) palladium (II) dichloride and a base e.g. sodium carbonate. The reaction is preferably carried out in a solvent e.g. hydrocarbon such as toluene and with heating.

Compounds of formula (I) wherein R_3 or R_6 is alkoxy e.g. methoxy may be prepared by treating the corresponding compound wherein R_3 and or R_6 is halogen e.g. chlorine or bromine with the appropriate alkanol e.g. methanol in the presence of a base such as sodium hydroxide.

Compounds of formula (I) which contain a phenyl group substituted by a methoxy group, as a substituent or part of a substituent may be converted into the corresponding compound of formula (I) wherein the phenyl group is substituted by hydroxy, by reaction with boron tribromide in a suitable solvent such as dichloromethane.

Compounds of formula (I) wherein R_2 is a phenyl group substituted by dialkylaminoalkoxy group may be prepared by reacting the corresponding compound of formula (I) wherein R_2 is a phenyl group substituted by hydroxy with a suitable base e.g. sodium hydride in an aprotic solvent such as dimethylformamide and then the appropriate dialklaminoalkylhalide.

Compounds of formula (I) wherein X_1 is CR_3 and R_3 is bromine may be converted into the corresponding wherein R_3 is formyl by reaction with n-butyllithium and dimethylformamide in a solvent such as tetrahydrofuran followed by quenching with water.

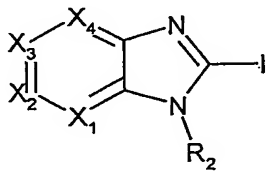
Compounds of formula (I) wherein R_3 is a methyl group substituted by a group selected from $R_{19}NH$,$R_{19}R_{20}N$, or an N linked, 4-7 membered heterocyclic group (containing one or two hetero atoms selected from N, O or S(O)n), may be prepared by reacting the corresponding compound wherein R_3 is formyl with the appropriate $R_{19}R_{20}NH$ or 4-7 membered heterocycle under reductive alkylation conditions. For example using a cyanoborohydride in a suitable solvent e.g. methanol. In this reaction if the groups R_{19},R_{20} or the 4-7 membered heterocycle contains an additional primary or secondary amino group then it is desirable to protect these using a conventional nitrogen protecting group such as a t-butyloxycarbonyl which may then be deprotected if so required.

In the above synthesis of compounds of formula (I) wherein they contain a primary or secondary amino grouping it may be necessary or desirable to carry out these procedures wherein the primary or secondary amine is in a protected form e.g. as a carbamate e.g. a t-butyl carbamate and then the carbamate converted into the required amine by conventional procedures, for example by the reaction with trifluoroacetic acid.

The nitrile of formula (VII) may be prepared by heating of a compound of formula (II) with ethyl cyanoacetate.

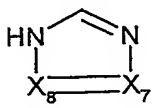
The compound of formula (VIII) may be prepared by reacting the nitrile of formula (VII) with an acetal of N, N dimethylformamide in a solvent e.g. a hydrocarbon such as ortho xylene and with heating.

Compounds of formula (VI) may be prepared by reaction of the 2-iodo-imidazole derivative (IX)



(IX)

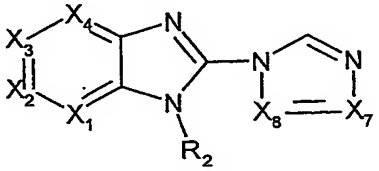
wherein R_2, X_1, X_2, X_3 and X_4 have the meanings defined in formula (I) with the compound (X)



(X)

wherein X_7 and X_8 have the meanings defined in formula (I)

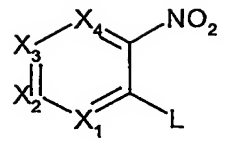
in the presence of a base and a polar aprotic solvent and then reacting the resultant compound (XI)



(XI)

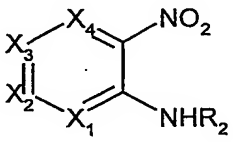
with an alkyl nitrite in the presence of a suitable base.

Compounds of formula (II) may be prepared by reacting a compound of formula (XII)



(XII)

wherein X_1, X_2, X_3 and X_4 have the meanings defined above and L is a group displaceable by the amine R_2NH_2 e.g. methoxy, bromine, chlorine, fluorine or methoxysulphonyl to give the nitro amine (XIII)



(XIII)

followed by reduction of the nitro group by conventional means, for example using hydrogen and a pal[illegible]on and an organic acid e.g. acetic acid or with sodium dithionate.

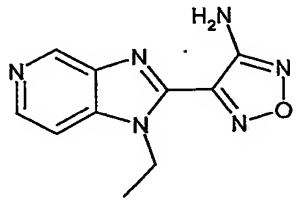
When compounds of formula (I) contain an asymmetric centre the specific enantiomers arising there from may be obtained by conventional procedures. For example using preparative high performance liquid chromatography (HPLC) with a chiral stationary phase.

Physiologically acceptable acid addition salts of the compounds of formula (I) may be prepared by conventional procedures, for example by addition of a solution of the inorganic or organic acid in a suitable solvent e.g. an alkanol or an ether to a solution of the free base in a solvent such as an alkanol, e.g. methanol or an ether e.g. diethyl ether or tetrahydrafuran.

The compounds of formula (III), (IV), (V) (IX), (X) and (XII) are either known compounds or may be prepared by analogous methods to those preparing the known compounds.

The following examples are illustrative of the present invention and are not to be construed as a limitation of the scope of the invention.

Example 1: 4-(1-Ethyl-1*H*-imidazo[4,5-*c*]pyridin-2-yl)furazan-3-ylamine



Step 1. Ethyl-(3-nitropyridin-4-yl)amine

4-Methoxy-3-nitropyridine hydrochloride (11.2g, 58.9mmol) in ethanol (75ml) was treated with a 70% solution of ethylamine in water (32ml) and heated under reflux for 1 hour. Further ethylamine solution (32ml) was added and the mixture heated under reflux for a further 2 hours. After cooling to room temperature, the solvent was removed *in vacuo* and the residue dissolved in ethyl acetate, washed (x3) with water and saturated aqueous sodium chloride solution, dried over sodium sulphate and concentrated *in vacuo* to afford the title compound (8.7g, 88%); MS (ES+) m/e 168 $[M+H]^+$.

Step 2. N^4-Ethylpyridine-3,4-diamine

The product from Step 1 (8.7g, 52.0mmol) in ethanol (150ml) was hydrogenated for 18 hours in the presence of 10% palladium on carbon. After filtration of the catalyst through

Kieselguhr, the filtrate was concentrated *in vacuo* to afford the title compound (6.7g, 94%); MS (ES+) m/e 138 $[M+H]^+$.

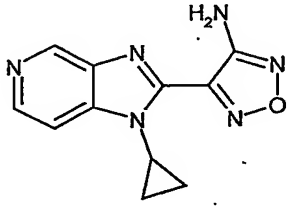
Step 3. (1-Ethyl-1*H*-imidazo[4,5-*c*]pyridin-2-yl)acetonitrile

The product from Step 2 (500mg, 3.6mmole) and ethyl cyanoacetate (620mg, 5.5mmol) were heated together at 190°C for 20 minutes. After cooling to room temperature, the residue was purified by column chromatography eluting with 10% methanol in ethyl acetate to afford the title compound (250mg, 37%); MS (ES+) m/e 187 $[M+H]^+$.

Step 4. 4-(1-Ethyl-1*H*-imidazo[4,5-*c*]pyridin-2-yl)furazan-3-ylamine

The product from Step 3 (200mg, 1.1mmol) im methanol (4ml) and 2N hydrochloric acid (4ml) was treated portionwise with sodium nitrite (150mg, 2.2mmol) and stirred at ambient temperature for 2 hours. The pH of the mixture was adjusted to 12 by addition of sodium hydroxide solution and a 50% solution of hydroxylamine in water (3ml) was added. The mixture was heated at 90°C for 2.5 hours and the reaction allowed to cool to room temperature. The resulting precipitate was filtered and dried *in vacuo* to afford the title compound (110mg, 43%); MS (ES+) m/e 231 $[M+H]^+$.

Example 2: 4-(1-Cyclopropyl-1*H*-imidazo[4,5-*c*]pyridin-2-yl)furazan-3-ylamine



Step 1. Cyclopropyl-(3-nitropyridin-4-yl)amine

4-Methoxy-3-nitropyridine hydrochloride (2.0g, 11.3mmol) and cyclopropylamine (1.6ml, 22.6mmol) in ethanol (5ml) was treated with triethylamine (1.7ml, 12.4mmol) and heated under reflux for 18 hours. After cooling to room temperature, the solvent was removed *in vacuo* and the residue dissolved in dichloromethane, washed with water and saturated aqueous sodium chloride solution, dried over magnesium sulphate and concentrated *in vacuo* to afford the title compound (1.7g, 84%); MS (AP+) m/e 180 $[M+H]^+$.

Steps 2. 4-(1-Cyclopropyl-1*H*-imidazo[4,5-*c*]pyridin-2-yl)furazan-3-ylamine

The title compound was prepared from the product of Step 1 using the methods of Example 1 Steps 2-4; MS (AP+) m/e 243 $[M+H]^+$.

The following examples were prepared by the general two-step method described in Example 2.

	Example	Amine	Characterisation
3	4-(1-Methyl-1*H*-imidazo[4,5-*c*]pyridin-2-yl)furazan-3-ylamine	Methylamine (8M in ethanol)	MS(AP+) m/e 217 $[M+H]^+$
4	4-(1-Cyclohexyl-1*H*-imidazo[4,5-*c*]pyridin-2-yl)furazan-3-ylamine	Cyclohexylamine	MS (ES+) m/e 285 $[M+H]^+$.

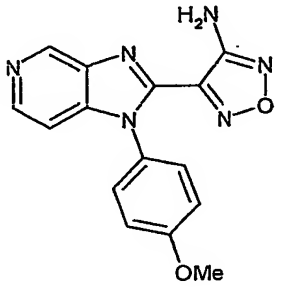
5	4-(1-Cyclopropylmethyl-1*H*-imidazo[4,5-*c*]pyridin-2-yl)furazan-3-ylamine	Cyclopropylmethylamine	MS(AP+) m/e 257 $[M+H]^+$
6	4-(1-Cyclohexylmethyl-1*H*-imidazo[4,5-*c*]pyridin-2-yl)furazan-3-ylamine	Cyclohexylmethylamine	MS(AP+) m/e 299 $[M+H]^+$
7	4-(1-Cyclobutyl-1*H*-imidazo[4,5-*c*]pyridin-2-yl)furazan-3-ylamine	Cyclobutylamine	MS(AP+) m/e 257 $[M+H]^+$
8	4-[1-(2-Ethylbutyl)-1*H*-imidazo[4,5-*c*]pyridin-2-yl)furazan-3-ylamine	2-Ethyl-*N*-butylamine	MS(AP+) m/e 288 $[M+H]^+$
9	4-(-Isopropyl-1*H*-imidazo[4,5-*c*]pyridin-2- yl)furazan-3-ylamine	Isopropylamine	MS(AP+) m/e 245 $[M+H]^+$
10	4-(1-*sec*-Butyl-1*H*-imidazo[4,5-*c*]pyridin-2-yl)furazan-3-ylamine	*sec*-Butylamine	MS(AP+) m/e 259 $[M+H]^+$
11	4-(1-Cyclopentyl-1 *H*-imidazo[4,5-c] pyridin-2-yl)-	Cyclopentylamine	MS(AP+) m/e 271 $[M+H]^+$
12	4-(1-Cycloheptyl-1 *H*-imidazo[4,5-c] pyridin-2-yl-furazan-3-ylamine	Cycloheptylamine	MS(AP+) m/e 299 $[M+H]^+$

13	4-[1-(2-Dimethylamino-1-methylethyl)-1*H*-imidazo[4,5-*c*]pyridin-2- yl)furazan-3-ylamine	N^1,N^1-Dimethyl-1,2-propanediamine	MS(AP+) m/e 288 $[M+H]^+$
14	4-(1-Piperidin-4-yl *H*-imidazo[4,5-c] pyridin-2-yl-furazan-3-ylamine	4-Amino-piperidine-1-carboxylic acid *tert*-butyl ester	MS(AP+) m/e 286 $[M+H]^+$
15	4-[1-(4-Diethylamino-1-methyl-butyl)-1 *H* -imidazo[4,5- *c*]pyridin-2-yl]-furazan-3-ylamine	2-amino-5-diethylamino pentane	MS (AP+) m/e 344 $[M+H]^+$
	(4-Amino-furazan-3-yl)-imidazo[4,5-*c*]pyridin-1-yl]-butyl}-carbamic acid tert-butyl ester	(4-Amino-butyl)-carbamic acid tert -butyl ester	MS (ES+) m/e 374 $[M+H]^+$

Examples 17 and 18: (+)-4-[1-(Dimethylaminomethylethyl)-1*H*-imidazo[4,5-*c*]pyridin-2- yl)furazan-3-ylamine and (-)-4-[1-(Dimethylaminomethylethyl)-1-*H*-imidazo[4,5-*c*]pyridin-2- yl)furazan-3-ylamine

The racemic product of Example 13 was separated into the title enantiomeric forms by preparative LC using Chiralcel OD, 10 micron particle size; 250 mm x 4.6 mm i.d.; n-Hexane : Ethanol, 99.7% v/v - 100% v/v (80:20 v/v); 1.0 ml/min; UV detection at 215 nm yielding the (+) enantiomer $[\alpha]_D$ + 6.8° ; HPLC tR 8.2min and the (-) enantiomer $[\alpha]_D$ –2.2°; HPLC tR 9.0min.

Example 19: 4-[1-(4-Methoxy-phenyl)-1*H*-imidazo[4,5-*c*]pyridin-2-yl]-furazan-3-ylamine



Step 1: (4-Methoxy-phenyl)-(3-nitro-pyridin-4-yl)-amine

To a solution of 4-chloro-3-nitropyridine (Kruger J, Mann F.G, *J. Chem. Soc.*, 1955, 2755) (700mg, 4.41mmol) in ethanol (10ml) was added 4-methoxyaniline (1.087g, 8.82mmol), followed by sodium acetate (362mg, 4.41mmol). The mixture was heated under reflux for 16 hours, cooled to room temperature and diluted with water (30m[illegible] resulting precipitate was collected by filtration, washed with water (x3) and dried *in vacuo* to afford the title product (800mg, 74%). MS (ES+) m/e 246 $[M+H]^+$.

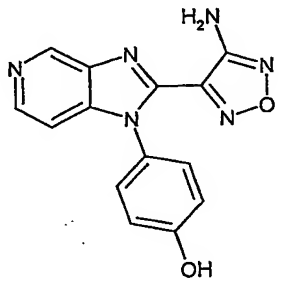
Step 2: 4-[1-(4-Methoxy-phenyl)-1H-imidazo[4,5-c]pyridin-2-yl]-furazan-3-ylamine

The title compound was prepared from the product of Step 1 using the methods of Example 1 Steps 2-4; MS (AP+) m/e 243 $[M+H]^+$.

The following examples were prepared by the general two-step method described in Example 19.

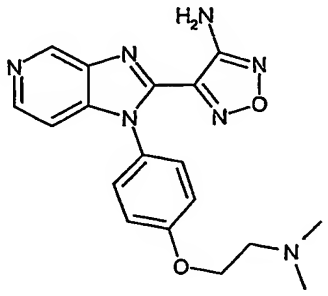
	Example	Aniline	Characterisation
20	4-(1-Phenyl-1 *H* -imidazo[4,5- *c*]pyridin-2-yl)-furazan-3-ylamine	Aniline	MS (ES+) m/e 279 $[M+H]^+$
21	4-[1-(4-Amino-phenyl)-1H-imidazo[4,5-*c*]pyridin-2-yl]-furazan-3-ylamine	4-amino acetanilide	MS (ES+) m/e 294 $[M+H]^+$

Example 22: 4-[2-(4-Amino-furazan-3-yl)-imidazo[4,5-c]pyridin-1-yl]-phenol



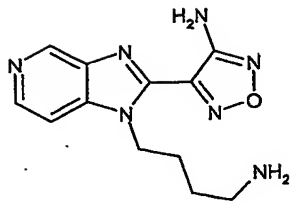
To a solution of Example 19 (100mg, 0.32mmol) in anhydrous dichloromethane (10ml) stirred at 0°C, was added dropwise boron tribromide (1.0 M solution in dichloromethane, 2.91ml, 2.92mmol) and the mixture stirred at room temperature for 16 hours. The reaction was quenched with water (20ml), basified to pH 14 with 50% sodium hydroxide solution. The aqueous phase was washed with dichloromethane (x3), neutralised with 5N hydrochloric acid, and the resulting precipitate collected, washed with water (x3), diethyl ether and dried *in vacuo* to yield the title product (59mg, 62%). MS (ES+) m/e 295 $[M+H]^+$.

Example 23: 4-{1-[4-(2-Dimethylamino-ethoxy)-phenyl]-1 *H* -imidazo[4,5- *c*]pyridin-2-yl}-furazan-3-ylamine hydrochloride



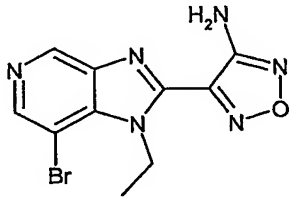
To a solution of the product of Example 22 (30mg, 0.102mmol), in *N,N*-dimethylformamide (2ml), was added sodium hydride (60% dispersion in oil, 4mg, 0.10mmol). After 5 minutes at room temperature 2-(dimethylamino)ethyl chloride hydrochloride (15mg, 0.102mmol) and sodium hydride (4mg, 0.102mmol) were added and the reaction heated at 60°C for 3 hours. The solvent was evaporated *in vacuo* to yield a residue which was partitioned between ethyl acetate and 2M sodium hydroxide solution. The organic phase was washed with water (x3), dried over anhydrous sodium sulphate and evaporated *in vacuo*. Purification of the residue by silica gel chromatography eluting with 10% methanol in dichloromethane gave the free base of the title compound. The product was dissolved in methanol (1ml) and treated with hydrochloric acid (1M solution diethyl ether, 36ul, 0.036mmol) and evaporated *in vacuo* to yield the title compound (14mg, 32%). MS (ES+) m/e 366 $[M+H]^+$.

Example 24: 4-[1-(4-Amino-butyl)-1 *H* -imidazo[4,5- *c*]pyridin-2-yl]-furazan-3-ylamine



A solution of the product of Example 16 (155mg, 0.415mmol) in anhydrous dichloromethane (4ml) was treated with trifluoroacetic acid (4ml), and stirred at room temperature for 0.5 hours. The solvent was evaporated *in vacuo* and the residue partitioned between dichloromethane and saturated sodium bicarbonate solution. The organic phase was washed with water (x3), and dried over anhydrous sodium sulphate, and the solvent evaporated *in vacuo*. The residue was purified by silica gel [illegible] eluting with a mixture of 0.880 ammonia:methanol:dichloromethane (1:9:90) to afford the title product (52mg, 46%). MS (ES+) m/e 274 $[M+H]^+$.

Example 25: 4-(7-Bromo-1-ethyl-1*H*-imidazo[4,5-*c*]pyridin-2-yl)furazan-3-ylamine



Step 1. (3-Bromo-5-nitropyridin-4-yl)ethylamine

To a solution of the product of Example 1 Step 1 (3.0g, 17.9mmol) in acetic acid (40ml) was added bromine (3.12g, 1ml, 19.7mmol) and the mixture was heated at 100°C for 20 hours. After cooling the solvent was removed *in vacuo* and the residue was partitioned

between dichloromethane and saturated sodium bicarbonate solution. The organic phase was washed with water (x3), dried and evaporated *in vacuo*. Purification of the residue by silica gel chromatography eluting with 50% dichloromethane in ethyl acetate afforded the title compound (1.9g, 43%). ^{1}H NMR (DMSO-d_6) 8.73 (1H, s), 8.52 (1H, s), 7.0 (1H, br), 3.25 (2H, m), 1.16 (3H, t, J 7.2Hz).

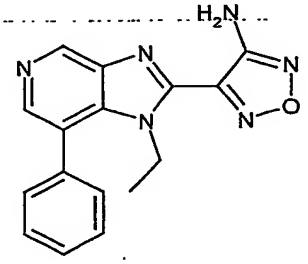
Step 2. 5-Bromo-N^4-Ethylpyridine-3,4-diamine

A solution of the product of Step 1 (0.5g, 2mmol) in ethanol (8ml) / water (10ml) was stirred at 60°C and sodium dithionite (2.12g, 12.2mmol) was added protionwise. After 10 minutes the mixture was cooled to room temperature, and diluted with water and dichloromethane. The organic phase was dried and evaporated *in vacuo*, the residue was used directly in the next reaction; ^{1}H NMR (DMSO-d_6) 7.76 (1H, s), 7.75 (1H, s), 5.0 (2H, br), 4.46 (1H, t, J9.6Hz), 3.26 (2H, m), 1.06 (3H, t, J7.2Hz).

Step 3. 4-(7-Bromo-1-ethyl-1*H*-imidazo[4,5-*c*]pyridin-2-yl)furazan-3-ylamine

The title compound was prepared from the product of Step 2 using the methods of Example 1 Steps 3 and 4; MH (ES+) m/e 309/311 $[M+H]^+$.

Example 26: 4-(1-Ethyl-7-phenyl-1*H*-imidazo[4,5-*c*]pyridin-2-yl)furazan-3-ylamine



A mixture of the product of Example 25 (50mg, 0.161mmol), phenylboronic acid (30mg, 0.243mmol), bis(triphenylphosphine)palladium (II) dichloride (11mg, 0.0161mmol), sodium carbonate solution (2M, 0.25ml) and toluene (3ml) was heated at 100°C for 3 hours. After cooling to room temperature the solvent was evaporated *in vacuo* and the residue purified by silica gel chromatography eluting with 50% dichloromethane in ethyl acetate to afford the title compound; (45mg, 92%). MS (ES+) m/e 307 $[M+H]^+$.

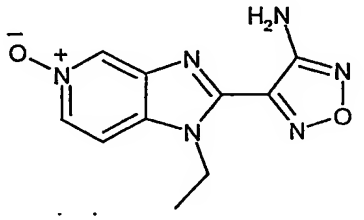
The following examples were prepared by the general method described in Example 26.

	Example	Boronic acid	Characterisation
27	4-[1-Ethyl-7-(4-methoxyphenyl)-1*H*-imidazo[4,5-*c*]pyridin-2-yl]furazan-3-ylamine	4-Methoxyphenylboronic acid	MS(ES+) m/e [illegible]$^+$
28	4-(1-Ethyl-7-thiophen-2-yl-1*H*-imidazo[4,5-*c*]pyridin-2-yl)furazan-3-ylamine	Thiophene-2-boronic acid	MS (ES+) m/e 313 $[M+H]^+$.

The following example were prepared by the general method described in Example 26, replacing the toluene solvent by 1,2-dimethoxyethane.

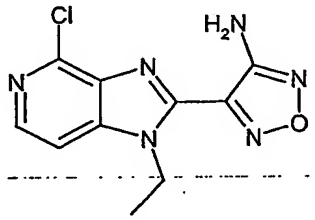
29	4-[7-(4-Aminomethylphenyl)-1-ethyl-1*H*-imidazo[4,5-*c*]pyridin-2-yl]furazan-3-ylamine	4-(Aminomethyl)-phenylboronic acid hydrochloride	MS (AP+) m/e 336 $[M+H]^+$.

Example 30: 4-(1-Ethyl-5-oxy-1*H*-imidazo[4,5-*c*]pyridin-2-yl)furazan-3-ylamine



A solution of the product of Example 1 (200mg, 0.869mmol) in acetic acid (2ml) was treated with hydrogen peroxide (30%, 0.108mg, 0.957mmol) and the mixture heated 90°C for 5 hours. After cooling to room temperature the mixture was poured into sodium carbonate solution and extracted with dichloromethane (x4). The organic phase was dried, the solvent was evaporated in vacuo and the residue purified by silica gel chromatography eluting with 15% methanol in dichloromethane, to afford the title compound (130mg, 53%); MS (ES+) m/e 247 $[M+H]^+$.

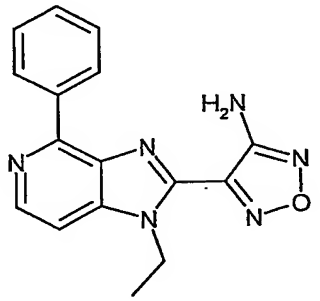
Example 31: 4-(4-Chloro-1-ethyl-1*H*-imidazo[4,5-*c*]pyridin-2-yl)furazan-3-ylamine



A solution of the product of Example 30 (80mg, 0.325mmol) in phosphorus oxychloride (4ml) was heated at 120°C for 6 hours. After cooling to room temperature the mixture

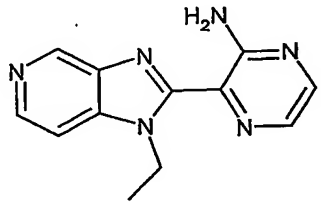
was concentrated *in vacuo* and the residue partitioned between dichloromethane and saturated sodium hydrogen carbonate solution. The organic phase was dried and the solvent was evaporated *in vacuo* to afford the title compound (81mg, 100%) which was used directly in the next reaction; MS (ES+) m/e 265/267 $[M+H]^+$.

Example 32: 4-(1-Ethyl-4-phenyl-1*H*-imidazo[4,5-*c*]pyridin-2-yl)furazan-3-ylamine



The title compound was prepared from the product of Example 30 and phenylboronic acid by the general method described in Example 26. MS (ES+) m/e 307 $[M+H]^+$.

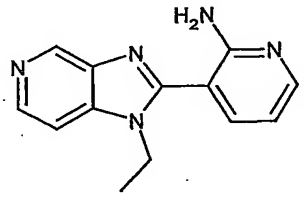
Example 33: 3-(1-Ethyl-1 *H*-imidazo[4,5-*c*]pyridin-2-yl)-pyrazin-2-ylamine



To polyphosphoric acid, preheated to 130°C, was added in one portion an intimate mixture of the product of Example 1 Step 2 (206 mg, 1.5 mmol) and 3-aminopyrazine-2-carboxylic acid (230 mg, 1.65 mmol). The temperature was increased to195°C for 1 hour

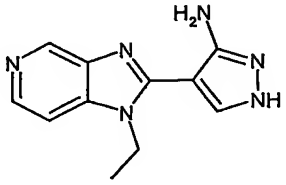
and then cooled back to 130°C for a further 1 hour. The viscous oil was poured on to ice containing saturated sodium carbonate solution and diethyl ether (5 ml) and the aqueous solution was extracted with chloroform (x5). The combined organic extracts were washed with brine, dried over anhydrous magnesium sulfate and concentrated *in vacuo*.. The crude solid was purified by silica gel chromatography eluting with a gradient of dichloromethane to 0.880 ammonia:ethanol:dichloromethane (1:9:40), to afford the title compound, (20mg, 6%); MS(ES+) m/e 241 $[M+H]^+$.

Example 34: 3-(1-Ethyl-1 *H*-imidazo[4,5-*c*]pyridin-2-yl)-pyridin-2-ylamine



The title compound was prepared from the product of Example 1 Step 2 and 2-aminonicotinic acid by the method described in Example 33; MS(ES+) m/e 240 $[M+H]^+$.

Example 35: 4-(1-Ethyl-1*H*-imidazo[4,5-*c*]pyridin-2-yl)-1*H*-pyrazol-3-ylamine



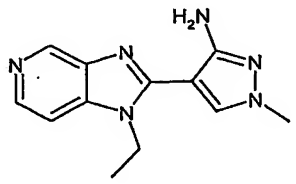
Step 1. Dimethylamino-(1-ethyl-1*H*-imidazo[4,5-*c*]pyridin-2-yl)-acrylonitrile

The product of Example 1 Step 3 (334mg, 1.8mmol) and *N,N*-dimethylformamide dimethylacetal (214mg, 1.8mmol) in *ortho*-xylene (4ml) was heated under reflux for 45 min. After cooling, the solution was concentrated and the residue co-evaporated with toluene (x3) to afford the title compound which was used directly in the next step; MS (ES+) m/e 242 $(M+H)^+$.

Step 2. 4-(1-Ethyl-1*H*-imidazo[4,5-*c*]pyridin-2-yl)-1*H*-pyrazol-3-ylamine

The product of Step 2 (217mg, 0.9mmol) and hydrazine hydrate (90mg, 1.8mmol) in methanol (5ml) was heated under reflux for 5 hours. After cooling, the reaction mixture was concentrated and the residue purified by silica gel chromatography eluting with 0.880 ammonia:ethanol:dichloromethane (1:9:90), to afford the title compound (27mg, 13%); MS (ES+) m/e 229 $[M+H]^+$.

Example 36: 4-(1-Ethyl-1*H*-imidazo[4,5-*c*]pyridin-2-yl)-1-methyl-1*H*-pyrazol-3-ylamine



Step 1. 4-(Bromo-1-methyl-1*H*-pyrazol-3-yl)-carbamic acid *tert*-butyl ester

A solution of 4-bromo-1-methyl-1*H*-pyrazol-3-ylamine (2.1g, 11.9mmol), di-*tert*-butyl dicarbonate (5.2g, 23.9mmol), 4-(dimethylamino)pyridine (1.45g, 11.9mmol) in 1,2-

dichloroethane (30ml) was stirred at room temperature for 3 hours. The reaction mixture was concentrated and the residue dissolved in a mixture of methanol (15ml) and sodium hydroxide solution (2M, 7.5ml, 15mmol) and heated at 60°C for 2 hours. After cooling, the reaction mixture was concentrated and the residue partitioned between ethyl acetate and water. The organic phase was washed with water, brine, dried and concentrated *in vacuo*. The residue was purified by silica gel chromatography eluting with ethyl acetate, to afford the title compound, (1.44g, 44%); MS (AP-) m/e 275/277 $[M-H]^-$.

Step 2. 4-(Formyl-1-methyl-1*H*-pyrazol-3-yl)-carbamic acid *tert*-butyl ester

A solution of the product of Step 1 (1.4g, 5mmol) in tetrahydrofuran (30ml) at -78°C under argon atmosphere was treated dropwise with *n*-butyl lithium (4.4ml, 2.5M in hexanes, 11mmol). After stirring at -78°C for 30 minutes the reaction mixture was warmed to 0°C for 30 minutes and then cooled to -78°C. *N,N*-Dimethylformamide (438mg, 0.46ml, 6mmol) was added and the solution warmed to room temperature over 2 hours. Saturated ammonium chloride solution was added and the mixture was extracted with ethyl acetate. The organic phase was washed with water, brine, dried and concentrated *in vacuo*. The residue was purified by silica gel chromatography eluting with ethyl acetate, to afford the title compound, (120mg, 11%); ^{1}H NMR ($CDCl_3$) 9.76 (1H, s), 8.5 (1H, br), 7.70 (1H, s), 3.91 (3H, s), 1.52 (9H, s).

Step 3. [4-(1-Ethyl-1*H*-imidazo[4,5-*c*]pyridin-2-yl)-1-methyl-1*H*-pyrazol-3-yl]-carbamic acid *tert*-butyl ester

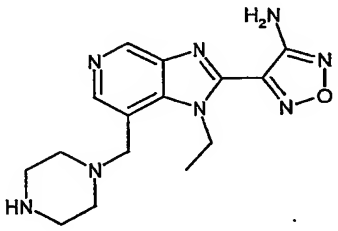
The product of Step 2 (110mg, 0.5mmol), the product of Example 1 Step 2 (68mg, 0.5mmol) and sodium hydrogen sulfite (208mg, 2mmol) in *N,N*-dimethylformamide (3ml) was heated at 120 °C for 2 hours. After cooling, the reaction mixture was

partitioned between dichloromethane and brine. The organic phase was washed with water, brine, dried and concentrated *in vacuo*. The residue was purified by silica gel chromatography eluting with 10% chloroform in methanol, to afford the title compound, (64mg, 53%); MS (ES+) m/e 343 $[M+H]^+$.

Step . 4-(1-Ethyl-1*H*-imidazo[4,5-*c*]pyridin-2-yl)-1-methyl-1*H*-pyrazol-3-ylamine

The product from Step 3 (58mg, 0.17mmol) was stirred in trifluoroacetic acid (0.5 ml) and dichloromethane (1ml) at room temperature for 1 hour and the solution was then co-evaporated three times with dichloromethane. The residue was purified by silica gel chromatography eluting with 0.880 ammonia:ethanol:dichloromethane (1:9:90), to afford the title compound, (29mg, 70%); MS (ES+) m/e 243 $[M+H]^+$.

Example [illegible]piperazin-1-ylmethyl-1H-imidazo[4,5-c]pyridin-2-yl)-furazan-3-ylamine



Step 1. 2-(4-Amino-furazan-3-yl)-1-ethyl-1*H*-imidazo[4,5-c]pyridine-7-carbaldehyde

A solution of the product from Example 25 Step 3 (0.1g, 0.324mmol) in tetrahydrofuran (4ml) at –78°C was treated with a 1.6M solution of n-butyllithium (0.6ml, 0.97mmol) in hexanes. After 5 minutes the mixture was treated with dimethylformamide (0.3ml) and allowed to reach room temperature. After 30 minutes at room temperature the reaction

was carefully quenched with water and extracted into dichloromethane (x2). The organic layer was then washed with brine, dried (Na_2SO_4) and reduced in vacuo. The residue was purified by silica gel chromatography eluting with ethyl acetate, to afford the title compound, (0.034g, 41%); MS (ES+) m/e 259 $[M+H]^+$.

Step 2. 4-[2-(4-Amino-furazan-3-yl)-1-ethyl-1-1*H*-imidazo[4,5-c]pyridin-7-ylmethyl]-piperazine-1-carboxylic acid *tert*-butyl ester

A solution of the product from Step 1 (0.05g, 0.194mmol) in methanol (2ml)was treated with piperazine-1-carboxylic acid *tert*-butyl ester (0.072g, 0.388mmol), (polystyrylmethyl)trimethylammonium cyanoborohydride (0.097g, 0.388mmol, 4mmol/g loading) and a few drops of glacial acetic acid. The mixture was stirred for 18 hours at room temperature and then filtered through celite and reduced *in vacuo*. The residue was purified by silica gel chromatography eluting with ethyl acetate, to afford the title compound, (0.035g, 42%); MS (ES+) m/e 429 $[M+H]^+$.

Step 3. 4-(1-Ethyl-7-piperazin-1-ylmethyl-1H-imidazo[4,5-c]pyridin-2-yl)-furazan-3-ylamine

A solution of the product from Step 2 (0.035g, 0.082mmol) in dichoromethane (1ml) was treated with trifluoroacetic acid (1ml). After 2 hours the reaction was reduced *in vacuo*, dissolved in methanol and applied to a SCX ion exchange column and eluted with methanol and then a mixture of methanol/0.880 ammonia (9:1). The basic fractions were then reduced to afford the title compound, (0.022g, 82%); MS (ES+) m/e 329 $[M+H]^+$.

The following examples were prepared from Example 37 Step 1 using the two-step method described in Example 37 Steps 2 and 3

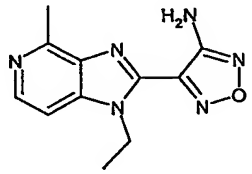
	Example	Amine	Characterisation
38	1-[2-(4-Amino-furazan-3-yl)-1-ethyl-1*H*-imidazo[4,5-c]pyridin-7-ylmethyl]-piperidin-4-ylamine	Piperidin-4-yl-carbamic acid *tert*-butyl ester	MS(ES+) m/e 343 $[M+H]^+$
39	[2-(4-Amino-furazan-3-yl)-1-ethyl-1*H*-imidazo[4,5-c]pyridin-7-ylmethyl]-piperidin-4-yl-amine	4-Amino-piperidine-1-carboxylic acid *tert*-butyl ester	MS (ES+) m/e 343 $[M+H]^+$

The following examples were prepared from Example 37 Step 1 using the method described in Example 37 Step 2

	Example	Amine	Characterisation
40	4-{7-[(4-Bromo-benzylamino)-methyl]-1-ethyl-1*H*-imidazo[4,5-c]pyridin-2-yl}-furazan-3-ylamine	4-Bromo-benzylamine	MS(ES+) m/e 429 $[M+H]^+$

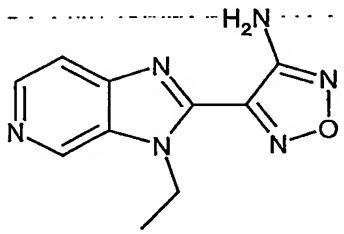
41	4-{1-Ethyl-7-[(3-methoxy-benzylamino)-methyl]-1*H*-imidazo[4,5-c]pyridin-2-yl}-furazan-3-ylamine	3-Methoxy-benzylamine	MS (ES+) m/e 380 $[M+H]^+$

Example 42: 4-(1-Ethyl-4-methyl-1*H*-imidazo[4,5-c]pyridin-2-yl)-furazan-3-ylamine



A solution of the product of Example 31 (0.1g, 0.377mmol) in 1,4-dioxan (8ml) was treated with a 2M solution of trimethylaluminium (0.378ml, 0.755mmol) in toluene and bis(triphenylphosphine)palladium (II) dich[illegible] 0377mmol). The mixture was heated at reflux for 4 hours and then coo[illegible] temperature, quenched carefully with water, poured into dichloromethane and washed with saturated sodium bicarbonate solution. The organic layer was then dried, reduced and the residue chromatographed on silica gel eluting with a mixture of dichloromethane and methanol (9.5/0.5) to afford the title compound, (0.022g, 13%); MS (ES+) m/e 245 $[M+H]^+$.

Example 37 : 4-(3-ethyl-3 *H*-imidazo[4,5-*c*]pyridin-2-yl)-furazan-3-ylamine



Step 1. Ethyl-(4-nitro-1-oxy-pyridin-3-yl)-amine

A solution of 3-bromo-4-nitropyrimidine-1-oxide (Daisley, R.W., Hanbali, J.R.; *Org. Prep. Proced. Int.*, 1983, **15**(4), 280) (8.1g, 37mmol) in chloroform (250ml) at 0°C was teated with ethylamine (70% aqueous solution, 25ml). After stirring at room temperature for 3 hours additional ethylamine solution (25ml) was added and stirring continued for a further 3 hours. The solution was concentrated *in vacuo* and the residue was purified by silica gel chromatography, eluting with a gradient of 10% ethylacetate/hexane to ethylacetate to afford the title compound, (3.68g, 54%); ^{1}H NMR ($CDCl_3$) □8.02 (1H, d, J 7.6Hz), 7.92 (1H, d, J 1.6Hz), 7.81 (1H, br s), 7.46(1H, dd, J=7.6, 1.6Hz), 3.32 (2H, m), 1.40 (3H, t, J 7.2Hz).

Step 2. *N*-3-ethyl-pyridine-3,4-diamine

The product of step 1 (3.68g, 20mmol) was dissolved in a 1:1 mixture of ethanol:tetrahydrofuran (300ml) and hydrogenated at room temperature and atmospheric pressure using raney nickel (ca. 1g) for 18 hours. The catalyst was removed by filtration on a filter aid pad and the filtrate concentrated *in vacuo* to afford the title compound which was used without further purification, (2.72g, 99%); ^{1}H NMR (DMSO) 7.53 (2H, m), 6.43 (1H, d, J 4.8Hz), 5.50 (2H, br s), 4.42 (1H, br s), 3.01 (2H, m), 1.21 (3H, t, J 7.2Hz)

Step 3. 3-ethyl-3H-imidazo[4,5-c]pyridin-2-yl)-acetonitrile

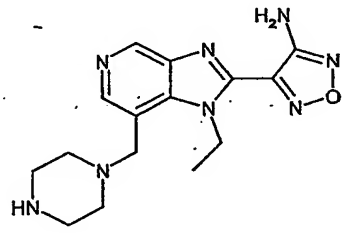
The title compound was prepared from the product of step 2 using the analogous procedure to that used in example 1, step3, (1.56g, 11mmol), affording (1.09g, 49%); ^{1}H

NMR ($CDCl_3$) 8.88 (1H d, J 0.8Hz), 8.49 (1H, d, J 5.6Hz), 7.68 (1H, dd, J 5.6, 0.8Hz), 4.38 (2H, q, J 7.4Hz), 4.13 (2H, s), 1.59 (3H, t, J 7.4Hz).

Step 4. 4-(3-ethyl-3H-imidazo[4,5-c]pyridin-2-yl)-furazan-3-ylamine

The title compound was prepared from the product of step 2 using the analogous procedure to that used in example 1, step 4, (1.03g, 5.5 mmol) affording (240mg, 49%); MS(ES+) m/e 231 $[M+H]^+$.

Example 37: 4-(1-Ethyl-7-piperazin-1-ylmethyl-1H-imidazo[4,5-c]pyridin-2-yl)-furazan-3-ylamine



Step 1. 2-(4-Amino-furazan-3-yl)-1-ethyl-1*H*-imidazo[4,5-c]pyridine-7-carbaldehyde

A solution of the product from Example 25 Step 3 (0.1g, 0.324mmol) in tetrahydrofuran (4ml) at –78°C was treated with a 1.6M solution of n-butyllithium (0.6ml, 0.97mmol) in hexanes. After 5 minutes the mixture was treated with dimethylformamide (0.3ml) and allowed to reach room temperature. After 30 minutes at room temperature the reaction was carefully quenched with water and extracted into dichloromethane (x2). The organic layer was then washed with brine, dried (Na_2SO_4) and reduced in vacuo. The residue was purified by silica gel chromatography eluting with ethyl acetate, to afford the title compound, (0.034g, 41%); MS (ES+) m/e 259 $[M+H]^+$.

Step 2. 4-[2-(4-Amino-furazan-3-yl)-1-ethyl-1-1*H*-imidazo[4,5-c]pyridin-7-ylmethyl]-piperazine-1-carboxylic acid *tert*-butyl ester

A solution of the product from Step 1 (0.05g, 0.194mmol) in methanol (2ml)was treated with piperazine-1-carboxylic acid *tert*-butyl ester (0.072g, 0.388mmol), (polystyrylmethyl)trimethylammonium cyanoborohydride (0.097g, 0.388mmol, 4mmol/g loading) and a few drops of glacial acetic acid. The mixture was stirred for 18 hours at room temperature and then filtered through celite and reduced *in vacuo*. The residue was purified by silica gel chromatography eluting with ethyl acetate, to afford the title compound, (0.035g, 42%); MS (ES+) m/e 429 $[M+H]^+$.

Step 3. 4-(1-Ethyl-7-piperazin-1-ylmethyl-1H-imidazo[4,5-c]pyridin-2-yl)-furazan-3-ylamine

A solution of the product from Step 2 (0.035g, 0.082mmol) in dichoromethane (1ml) was treated with trifluoroacetic acid (1ml). After 2 hours the reaction was reduced *in vacuo*, dissolved in methanol and applied to a SCX ion exchange column and eluted with methanol and then a mixture of methanol/0.880 ammonia (9:1). The basic fractions were then reduced to afford the title compound, (0.022g, 82%); MS (ES+) m/e 329 $[M+H]^+$.

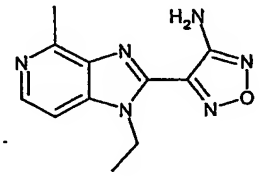
The following examples were prepared from Example 37 Step 1 using the two-step method described in Example 37 Steps 2 and 3

	Example	Amine	Characterisation
38	1-[2-(4-Amino-furazan-3-yl)-1-ethyl-1*H*-imidazo[4,5-c]pyridin-7-ylmethyl]-piperidin-4-ylamine	Piperidin-4-yl-carbamic acid *tert*-butyl ester	MS(ES+) m/e 343 $[M+H]^+$
39	[2-(4-Amino-furazan-3-yl)-1-ethyl-1*H*-imidazo[4,5-c]pyridin-7-ylmethyl]-piperidin-4-yl-amine	4-Amino-piperidine-1-carboxylic acid *tert*-butyl ester	MS (ES+) m/e 343 $[M+H]^+$

The following examples were prepared from [illegible] using the method described in Example 37 Step 2

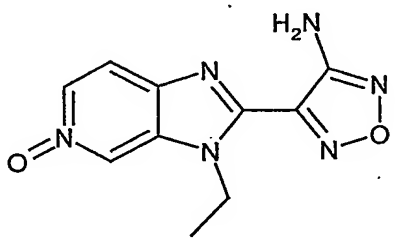
	Example	Amine	Characterisation
40	4-{7-[(4-Bromo-benzylamino)-methyl]-1-ethyl-1*H*-imidazo[4,5-c] pyridin-2-yl}-furazan-3-ylamine	4-Bromo-benzylamine	MS(ES+) m/e 429 $[M+H]^+$
41	4-{1-Ethyl-7-[(3-methoxy-benzylamino)-methyl]-1*H*-imidazo[4,5-c]pyridin-2-yl}-furazan-3-ylamine	3-Methoxy-benzylamine	MS (ES+) m/e 380 $[M+H]^+$

Example 42: 4-(1-Ethyl-4-methyl-1*H*-imidazo[4,5-c]pyridin-2-yl)-furazan-3-ylamine



A solution of the product of Example 31 (0.1g, 0.377mmol) in 1,4-dioxan (8ml) was treated with a 2M solution of trimethylaluminium (0.378ml, 0.755mmol) in toluene and bis(triphenylphosphine)palladium (II) dichloride (0.026g, 0.0377mmol). The mixture was heated at reflux for 4 hours and then cooled to room temperature, quenched carefully with water, poured into dichloromethane and washed with saturated sodium bicarbonate solution. The organic layer was then dried, reduced and the residue chromatographed on silica gel eluting with dichloromethane and methanol (9.5/0.5) to afford the title compound, (0.0[illegible]mS (ES+) m/e 245 $[M+H]^+$.

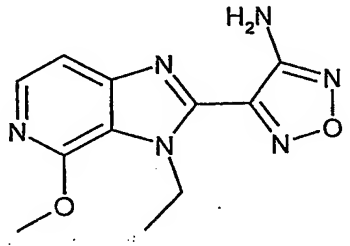
Example 43: 4-(3-Ethyl-5-oxy-3H-imidazo[4,5-c]pyridin-2-yl)-furazan-3-ylamine



The product of Example 37, Step 4 (362mg, 1.6mmol) in acetic acid (2ml) was treated with 30%wt aqueous solution of hydrogen peroxide (432mg, 3.1mmol) and the solution was heated at 80°C for 18 hours. After cooling to room temperature the mixture was

basified with solid sodium carbonate and extracted with chloroform (x5). The combined extracts were washed with brine, dried over anhydrous sodium sulfate and concentrated *in vacuo*. The residue was purified by column chromatography eluting with 0.880 ammonia:ethanol:dichloromethane (1:9:90) to afford the title product, (370mg, 96%); MS(ES+) m/e 247 $[M+H]^+$.

Example 44: 4-(3-ethyl-4-methoxy-3*H*-imidazo[4,5-*c*]pyridin-2-yl)-furazan-3-ylamine

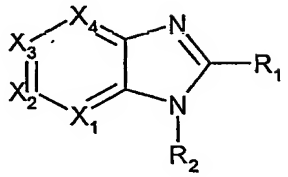


The product of Example 43 (370mg, 1.5mmol) in phosphorous oxychloride (5ml). was heated at reflux for 4 hours. The solution was cooled and co-evaporated with toluene, the residue was basified with ice cold sodium carbonate and the aqueous solution extracted with ethyl acetate (x3). The combined extracts were washed with brine, dried over anhydrous sodium sulfate and concentrated *in vacuo*. The residue was suspended in a solution of 50% sodium hydroxide (5ml), containing methanol (5ml) and heated at 80°C for 5 hours. The solution was concentrated *in vacuo* and the resulting wet solid that was extracted with ethyl acetate (x3). The combined extracts were washed with water (x2), brine, dried over anhydrous sodium sulfate and concentrated *in vacuo*. The residue was purified by column chromatography eluting with a gradient of dichloromethane to 0.880

ammonia:ethanol:dichlorormethane (1:9:90), to afford the title compound (30mg, 8%); MS(ES+) m/e 445 $[M+H]^+$.

Claims

1. A compound of the general formula (I)



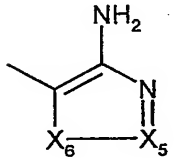
(I)

and physiologically acceptable salts and or N-oxides thereof wherein,

X_1 is N or CR_3; X_2 isN or CR_4; X_3 is N or CR_5; X_4 is N or CR_6.

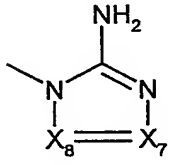
with the proviso that at least one but not more than two of X_1, X_2, X_3 and X_4 represents N.

R_1 is a 5-, or 6- membered heterocyclic group selected from a group a, b, c or d



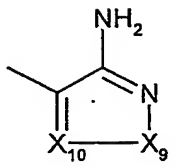
(a)

wherein X_5 is a group selected from N or CR_7 and X_6 is a group selected from O, S or NR_8;



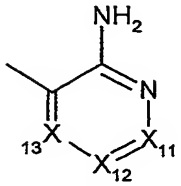
(b)

wherein X_7 and X_8 which may be the same or different is a group selected from N or CR_9;



(c)

wherein X_9 is a group selected from O, S or NR_8 and X_9 is N or CR_{10};



(d)

wherein X_{11}, X_{12} and X_{13} may be the same or different and selected from a group N or CR_{11};

R_2 and R_8 indepen[illegible]ydrogen, hydroxy, aryl, heteroaryl, C_{3-7}cycloalkyl, heterocyclyl, [illegible]YR_{12}, $N{=}R_{13}$, $CONR_{14}R_{15}$, $NHCOR_{16}$, $SO_2NR_{14}R_{15}$ or C_{1-6}alkyl [optionally substituted by a group selected from optionally substituted phenyl, C_{3-7}cycloalkyl, heteroaryl, heterocyclyl, acylamino, NH_2, $R_{19}NH$, $R_{19}R_{20}N$, $SO_2NR_{14}R_{15}$, $CONR_{14}R_{15}$, $NHCOR_{16}$ or $NR_{17}SO_2R_{18}$ group];

R_3, R_4, R_5,R_6,R_7,R_9,R_{10} and R_{11} independently represent a group selected from hydrogen, halogen, hydroxy, $R_{19}O$, $R_{19}S(O)_n$, NH_2, $R_{19}NH$, $R_{19}R_{20}N$, nitro, formyl, C_{1-4}alkanoyl, optionally substituted phenyl, heteroaryl, cycloalkyl, cycloalkylalkyl, aryloxy, heteroaryloxy, heterocyclyl, $CONR_{15}R_{13}$, $NHCOR_{16}$, $SO_2NR_{14}R_{15}$, $NR_{17}SO_2R_{18}$ or C_{1-6}alkyl [optionally substituted by a group selected from optionally substituted phenyl, C_{3-7}cycloalkyl, heteroaryl, heterocyclyl, NH_2, $R_{19}NH$, $R_{19}R_{20}N$, acylamino, hydroxy, $CONR_{14}R_{15}$, $NHCOR_{16}$, $SO_2NR_{14}R_{15}$ or $NR_{17}SO_2R_{20}$ group];

Y represents O, NH or $S(O)_n$;

R_{12} represents aryl, heteroaryl, cycloalkyl, heterocyclyl or C_{1-6}alkyl [optionally substituted by a group selected from optionally substituted phenyl, C_{3-7}cycloalkyl, heteroaryl, heterocyclyl, NH_2, $R_{19}NH$, $R_{19}R_{20}N$, acylamino, hydroxy, $CONR_{14}R_{15}$, $NHCOR_{16}$, $SO_2NR_{14}R_{15}$ or $NR_{17}SO_2R_{18}$ group];

R_{13} represents an alkylidene group which may be substituted by an aryl, heteroaryl, heterocyclyl or cycloalkyl group or R_{13} represents a cycloalkylidene or heterocycloalkylidene group.

R_{14} and R_{15} independently represent hydrogen, aryl, heteroaryl, cycloalkyl or C_{1-6}alkyl [optionally substituted by a group selected from optionally substituted phenyl, C_{3-7}cycloalkyl, heteroaryl, heterocyclyl, NH_2, $R_{19}NH$, $R_{19}R_{20}N$, or acylamino group] R_{15} together with the nitrogen atom to which they are attached form a 4-7 [illegible]c ring which may be saturated or unsaturated and optionally contains another heteroatom selected from O,N or $S(O)_n$;

R_{16} and R_{18} independently represent ,aryl, heteroaryl, heterocyclyl,cycloalkyl or C_{1-6}alkyl [optionally substituted by a group selected from optionally substituted phenyl, C_{3-7}cycloalkyl, heteroaryl, heterocyclyl, NH_2, $R_{19}NH$, $R_{19}R_{20}N$, or acylamino group] or the group $NR_{14}R_{15}$ wherein R_{14} and R_{15} have the meanings defined above;

R_{17} represents hydrogen, aryl, heteroaryl, cycloalkyl or C_{1-6}alkyl [optionally substituted by a group selected from optionally substituted phenyl, C_{3-7}cycloalkyl, heteroaryl, heterocyclyl, NH_2, $R_{19}NH$, $R_{19}R_{20}N$, or acylamino group];

R_{19} and R_{20} independently represent a group selected from C_{1-6} alkyl, C_{3-7}cycloalkyl, C_{3-7}cycloalkylalkyl, aryl, aralkyl, heteroaryl, heteroarylalkyl, heterocyclyl or heterocyclylalkyl;

n is zero, 1 or 2.

2. A compounds as claime in claim wherein only one of X_1, X_2, X_3 or X_4 represents N.

3. A compound as claimed in claim2 wherein X_2 or X_3 represent N .

4. A compound as claimed in any of claims 1 to 3 wherein X_3 represents N

5. A compound as claimed in claim 1 wherein X_1 and X_3 each represents N .

6. A compound as claimed in any of claims 1 to 5 wherein R_1 is a group selected from (c) or (d).

7. A compound as claimed in any of claims 1 to 6 wherein R_1 is a group (c) in which X_9 is oxygen and X_{10} is nitrogen

8. A compound as claimed in any of claims 1 to 7 wherein R_2 is a group selected from C_{1-6}alkyl, C_{3-7} cycloalkyl, C_{3-7}cycloalkylmethyl ,phenyl or phenyl (substituted by amino, diethylaminoethoxy, methoxy or hydroxy group), alkyl (substituted by acylamino, $R_{19}NH$, $R_{19}R_{20}N$ or hydroxy) or a heterocyclyl group .

9. A compound as claimed in any of claims 1 to 8 wherein X_2 is CR_4 and R_4 is hydrogen, alkyl or alkoxy.

10. A compound as claimed in any of claims 1 to 9 wherein X_3 is CR_5 and R_5 is hydrogen, alkyl or alkoxy.

11. A compound as claimed in any of claims 1 to 10 wherein X_4 is CR_6 and group R_6 is a group selected from hydrogen, halogen , alkyl, alkoxy, optionally substituted phenyl or a hetrocyclyl group..

12. A compound as claimed in any of claims 1 to 11 wherein X_1 is CR_3 and R_3 is a group selected from hydrogen, halogen , optionally substituted phenyl, heteroaryl, alkyl (substituted by the group $R_{19}NH$ or a heterocyclyl group) or a 6,5 fused bicycloheterocyclyl group.

13. A pharmaceutical formulation comprising a compound of formula (I) or a pharmaceutically acceptable salt and or an N oxide thereof together with one or more pharmaceutically acceptable excipients and /or carriers .

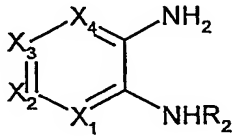
14. A compound of formula (I) and/or physiologically acceptable salts thereof for use in therapy .

15. The use of a compound of formula (I) and/or a physiologically acceptable salt thereof in the manufacture of a medicament for inhibiting the effects of the kinase Msk-1.

16. A method for inhibiting the effects of the kinase MSK-1 comprising administering to a patient in need thereof an effective amount of a compound of formula (I) and/or a physiologically acceptable salt thereof.

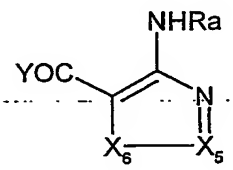
17. A process for preparing a compound of formula (I) which comprises :-

a) a process for preparing compounds of formula (I) wherein R1 is a group (a), (c) and (d) by reacting the diamine (II)

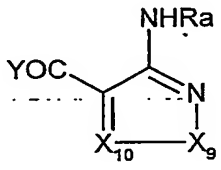


(II)

wherein R_2, X_1, X_2, X_3 and X_4 have the meanings defined in (I) with the appropriate compound of formula (III), (IV) or (V)



(III)



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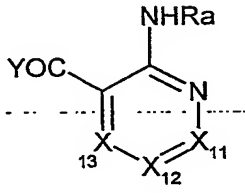
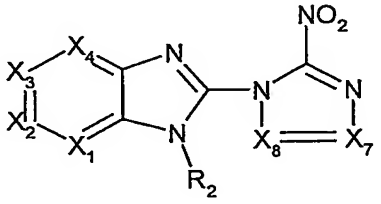


(V)

wherein Y is hydrogen , halogen e.g. Cl, Br or I, hydroxy or C_{1-4}alkoxy, Ra is hydrogen or a nitrogen protecting group such as an alkoxycarbonyl or benzyloxycarbonyl group and each of X_5, X_6, X_9, X_{10}, X_{11}, X_{12} and X_{13} have the meanings as defined in formula (I) or is a group available thereto, followed when required by removal of the nitrogen protecting group Ra using conventional methods.

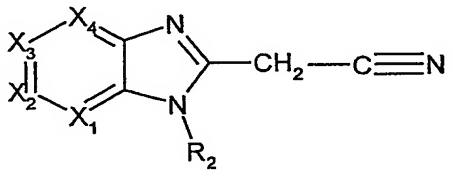
b) a process for preparing compounds of formula (I) wherein Y is the group (b) reducing of the corresponding nitro derivative (VI)



(VI)

wherein R_2, R_3, R_3, X_1, X_2, [illegible] have the meanings defined in formula (I).

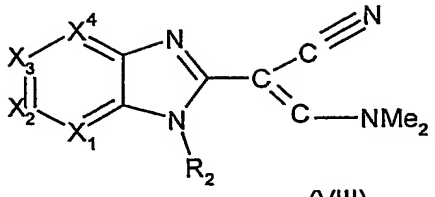
c) a process for the preparation compounds of formula (I) wherein R_1 is the group (c) and X_9 is oxygen and X_{10} is nitrogen may be prepared by reacting the nitrile (VII)



(VII)

wherein R_2, X_1, X_2, X_3 and X_4 have the meanings defined in formula (I) with hydrochloric acid and sodium nitrite in a solvent and treatment of the product thus formed with a and hydroxylamine.

d) a process for preparing a compounds of formula (I) wherein R_1 represent the group (c) and wherein X_9 is NH and X_{10} is CH may be prepared by reacting compound (VIII)

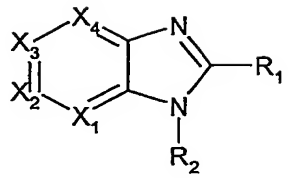


(VIII)

wherein R_2, X_1, X_2, X_3 and X_4 have the meanings defined in formula (I) with hydrazine.

Abstract

A compound of the general formula (I)



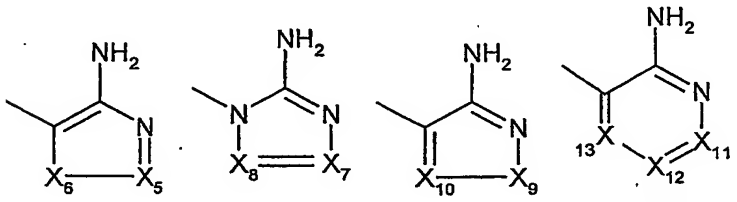
(I)

and physiologically acceptable salts and or N-oxides thereof wherein,

X_1 is N or CR_3; X_2 isN or CR_4; X_3 is N or CR_5; X_4 is N or CR_6.

with the proviso that at least one but not more than two of X_1, X_2, X_3 and X_4 represents N;

R_1 is a 5-, or 6- membered heterocyclic group selected from group a, b, c or d,



(a) (b) (c) (d)

processes for their preparation and their use in medicine.

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